Quality by Design (QbD)

What is Quality by Design?

Systematic approach to development

- Applies to both IND and NDA review
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

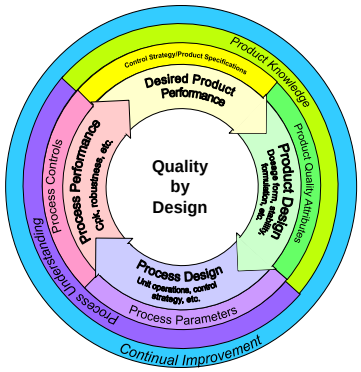
From ICH Q8(R1)

Why QbD?

- Higher level of assurance of product quality
- Cost saving and efficiency for industry
  - Facilitate innovation to address unmet medical needs
  - Increase efficiency of manufacturing process and reduce manufacturing cost and product rejects
  - Minimize/eliminate potential compliance actions, costly penalties and recalls
  - Opportunities for continual improvement
- More efficient regulatory oversight
  - Enhance opportunities for first cycle approval
  - Streamline post approval manufacturing changes and regulatory processes
  - More focused PAI and post approval cGMP inspections


Product Knowledge
Control Strategy/Specifications
Desired Product Performance
Product Quality Attributes
Process Controls
Process Performance
Cpk, robustness, etc.
Product Design
Dosage form, stability, formulation, etc.
Quality by Design
Process Design
Unit operations, control strategy, etc.
Process Understanding
Process Parameters
Continuous Improvement

QbD System



Define desired product performance upfront; identify product CQAs

Design formulation and process to meet product CQAs

Understand impact of material attributes and process parameters on product CQAs

Identify and control sources of variability in material and process

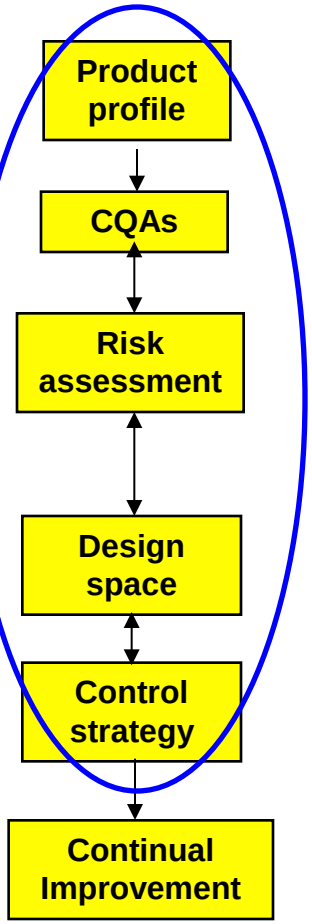
Continually monitor and update process to assure consistent quality

Risk assessment and risk control

Quality by Design (QbD) – A Comprehensive Systematic Approach to Pharmaceutical Development and Manufacturing

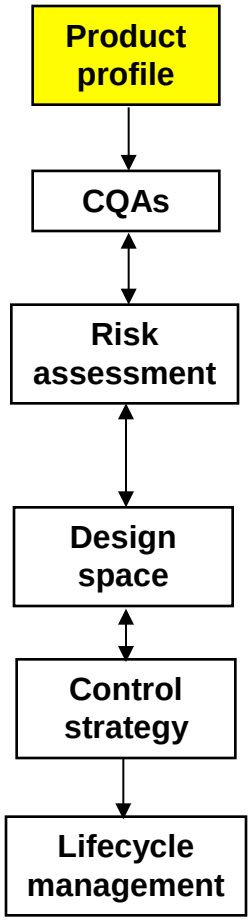
Aspects	Traditional	QbD
Pharmaceutical Development	**Empirical**; typically univariate experiments	**Systematic**; multivariate experiments
Manufacturing Process	**Fixed**	**Adjustable** within design space; opportunities for innovation **(PAT)**
Process Control	In-process testing for go/no-go; offline analysis w/ slow response	**PAT utilized** for feedback and feed forward at real time
Product Specification	Primary means of quality control; based on batch data	Part of the overall quality control strategy; based on desired product performance (safety and efficacy)
Control Strategy	Mainly by intermediate and end product testing	**Risk-based**; controls shifted upstream; real-time release
Lifecycle Management	**Reactive to problems** & OOS; post-approval changes needed	**Continual improvement** enabled within design space

Example QbD Approach (ICH Q8R1)



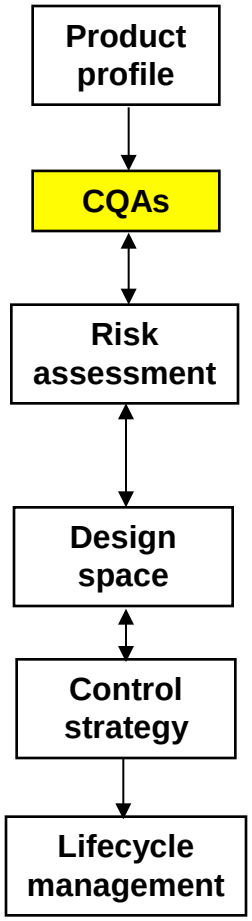
- Target product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Product Profile



- Product profile considerations
  - dosage form
  - strengths
  - route of administration
  - release/delivery and pharmacokinetic characteristics
  - specific quality criteria (e.g. sterility, purity)
- Dosage form examples
  - tablets
  - inhalation spray
  - parenteral

Critical Quality Attributes (CQAs)



- Definition (Q8R1)
  - A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality
- Can describe aspects of drug substance or intermediates that affect drug product quality
- Drug product CQAs are used to guide product and process development

Example of Critical Quality Attributes

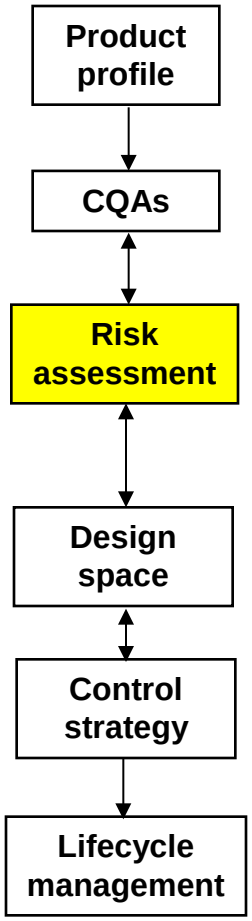
-CQA from clinical performance standpoint

- dissolution for extended-release product

-CQAs from processability standpoint

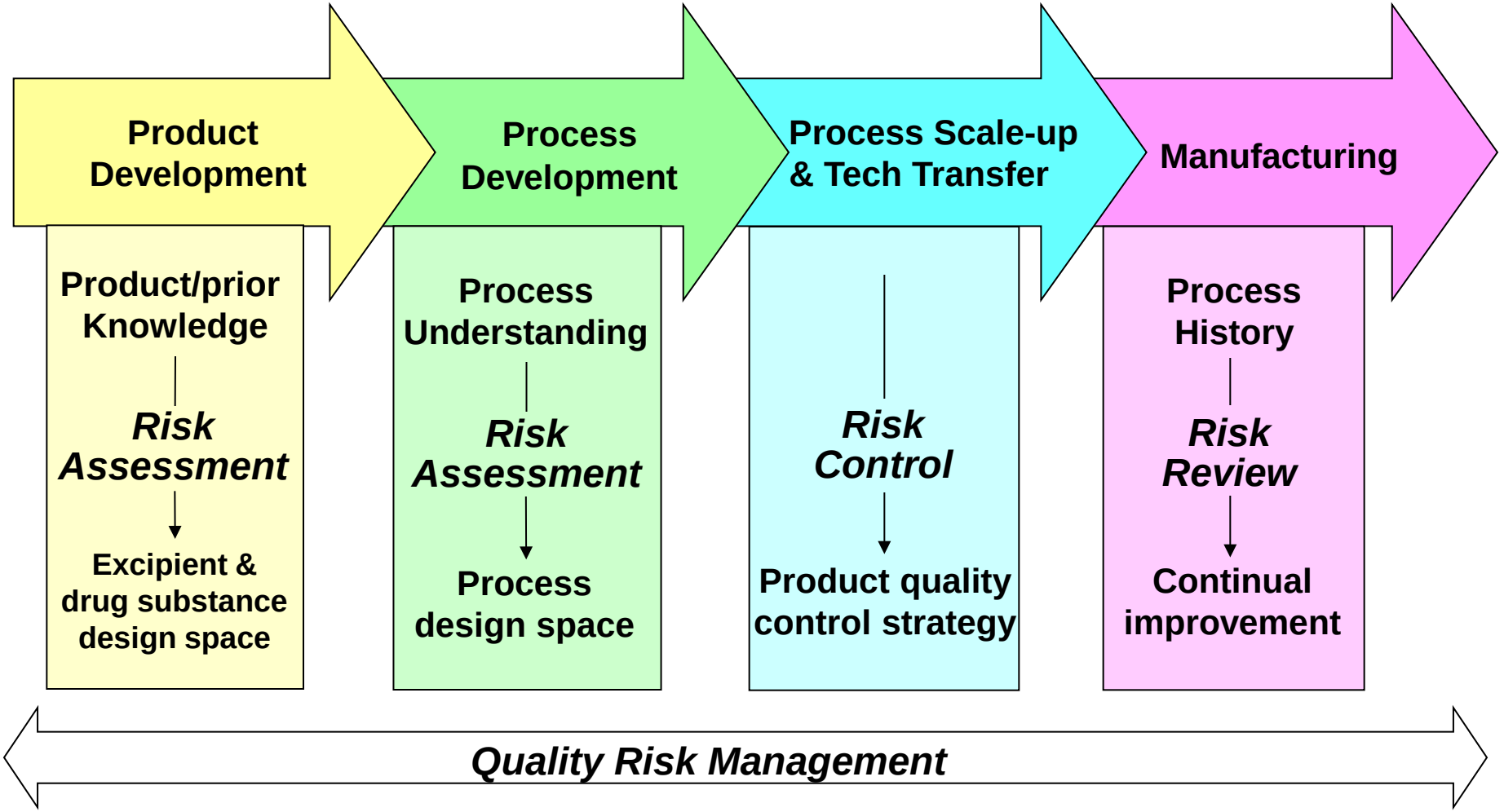
- tablet hardness
- particle size distribution of blend
- appearance

QbD – Risk Assessment (Q8R1)

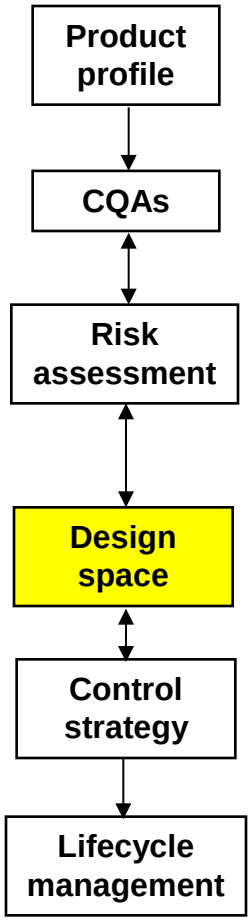


- Prioritize list of potential CQAs
- Aid in identifying and linking material attributes and process parameters which have an effect on CQAs

Quality Risk Management



QbD – Design Space (Q8R1)



- Definition
  - The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters.
- Regulatory flexibility
  - Working within design space is not considered a change
- Design space is proposed by the applicant and is subject to regulatory assessment and approval

Why QbD?

- Higher level of assurance of product quality
- Cost saving and efficiency for industry and regulators
  - Facilitate innovation to address unmet medical needs
  - Increase efficiency of manufacturing process and reduce manufacturing cost and product rejects
  - Minimize potential compliance actions, costly penalties and recalls
  - Enhance opportunities for first cycle approval
  - Streamline post approval manufacturing changes and regulatory processes
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  - Opportunities for continual improvement

When to do QbD?

Timing is at Applicant's discretion

- Phase 1: focus on product understanding
- Phase 2: focus on process understanding
- Phase 3: apply product and process understanding to manufacture of clinical trial supplies and NDA supportive batches

Agency interactions: EOP2, pre-NDA, CMC specific meetings (all are encouraged)

How Does QbD Accelerate Development?

More work upfront

- Systematic
- More thorough results
- Reduces product failures
- Quality control strategies based on product knowledge and process understanding
- A more scientific and risk-based approach to regulatory oversight

You cannot place a price tag on failures that do not occur.

FDASIA - Challenges for Quality Review

- Section 901– Fast Track Drug Products
  - Facilitate development and expedite the review of drugs for the treatment of a serious or life-threatening disease or condition that demonstrates the potential to address unmet medical need
- Section 902 –Breakthrough Therapy Drugs
  - Expedite the development and review of a drug for serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies
    - Provide timely advice and interactive communication with the sponsor regarding the development of the drug to ensure that the development proceeds as planned
    - Provide a collaborative cross disciplinary review utilizing senior managers and experienced review staff, as appropriate
- Section 905 – Risk Benefit Framework
  - Implement a structured risk-benefit assessment framework in the new drug approval process and regulatory decision making

Challenges for Expedited Reviews

- Alignment of CMC development and manufacturing timelines with the clinical development program
  - Consideration of manufacturing scale
  - Coordination with contract manufacturers, as needed
  - Early availability of manufacturing sites for inspection
- Coordination of CMC development program and submissions
  - Recommend early communication between Sponsor and Agency
  - Involve both review and compliance staff to facilitate review and inspection timing
  - Recommend earlier submission of product quality information for review and inspection planning
- Accelerated manufacturing development program likely with less information than typically available
  - May warrant a risk-benefit assessment regarding risk of less CMC information vs. patient benefit

Considerations for Expedited Reviews

- Limited data available and/or submitted
  - Manufacturing batch data
  - Stability data
  - Data available at time of submission
- Review timing constraints
- Frequent communication often needed
- Supply considerations

All rest on…What is the risk to overall quality?

Expedited Reviews – Best Practices

- Pre-NDA discussions
  - Clinical/commercial comparability
  - Stability data package to be submitted
  - Amount of stability data in original NDA
  - Manufacturing sites identified
  - Significant Quality by Design elements
  - Possible post-marketing CMC commitments/requirements
  - Availability of drug for commercial launch
- During the NDA review
  - Teleconferences as needed for clarification
  - Information Requests

Communications

- IND stage
  - preIND, EOP1, EOP2, preNDA
  - Sponsors can request additional meetings
  - CMC-specific meetings are an option
  - Formal Information Requests
  - For anticipated expedited/priority therapies, preNDA meetings can be used to discuss critical aspects of incoming NDA submission
- NDA stage
  - Formal Information Requests
  - PDUFA V (e.g. LCM)
  - Teleconferences during review clock, as needed

Proposed Office of Pharmaceutical Quality

- Combines components of current CDER Office of Pharmaceutical Sciences and CDER Office of Compliance
- Intended to provide better alignment between all quality functions (review, inspection, research)
- Focus areas for new office:
  - Integrated approaches for review and inspection
  - Risk based approaches to review and inspection
  - Efficiency and risk-based work prioritization
  - Modern regulatory science approaches (e.g., clinically relevant specifications, statistical sampling)

Conclusions

- CMC Clinical Hold recommendations (IND)
  - Based on unresolved CMC safety issues during an IND's safety review
  - Can also be based on safety issues identified during development
- CMC Refuse to File recommendations (NDA)
  - Based on an incomplete submission
  - Manufacturing and testing sites not ready for inspection at the time of NDA submission
  - Insufficient (or missing) stability data
- Quality by Design – a more scientific and risk-based approach to regulatory oversight
- Some challenges with expedited/priority therapies
  - Alignment of CMC and clinical development
  - Sometimes warrants a risk/benefit assessment regarding risk of less CMC information vs. patient benefit
- Proactive communications encouraged during development and review
- FDASIA and CDER's restructuring of quality functions hold promise for moving forward

Acknowledgements

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